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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,897	09/22/2006	Peter Wisdom Atadja	33310A	7190

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
03/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,897	ATADJA ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/09/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 21-24* is/are pending in the application.

4a) Of the above claim(s) *21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/09/2009 has been entered.

Status of Application

2. The Examiner acknowledges receipt of the amendments filed on 07/09/2009 wherein claims 1, 4-6 and 14 have been amended, claims 15-20 have been cancelled and claim 24 is newly added.

3. Claims 1, 2, 4-14 and 24 are presented for examination on the merits. The following rejections are made.

Response to Applicants' Arguments

4. Applicants arguments filed 07/09/2009 regarding the rejection of claim 3 made by the Examiner under 35 USC 112, first paragraph (written description) have been fully considered and they are found persuasive. This rejection has been overcome by cancellation of the claims.

5. Applicants arguments filed 07/09/2009 regarding the rejection of claim 3 made by the Examiner under 35 USC 103(a) over Remiszewski et al. (US 6552065) in view of Verner et al. (US 7276612) and Griffin et al. (US 2005/0020570) have been fully considered and they are found persuasive. This rejection has been overcome by cancellation of the claim.

6. Applicants arguments filed 07/09/2009 regarding the rejection of claim 1, 2 and 4-14 made by the Examiner under 35 USC 112, first paragraph (written description) have been fully considered but they are not found persuasive.

7. The rejection of claims 1, 2 and 4-14 made by the examiner under 35 USC 112, first paragraph is **MAINTAINED** for the reasons of record in the office action mailed on 01/05/2009.

8. In regards to the 112 rejection, Applicant asserts the following:

A) The rejection has been overcome by amendment to the claims, i.e. deleting the term prodrug.

9. In response to A, the Examiner thanks Applicant for removing the term 'prodrug' for the FLT-3 inhibitor compound. However, Applicant still has the HDAI component as encompassing prodrugs without adequately describing what a 'prodrug' encompasses. Since the specification (fails to provide specific disclosure on how to make a prodrug, or what modifications would result in a prodrug, Applicant is not found to have been in possession of the genus of HDAI prodrugs at the time the invention was filed.

10. Applicants arguments filed 07/09/2009 regarding the rejection of claim 1, 2 and 4-14 made by the Examiner under 35 USC 103(a) over Remiszewski et al. (US 6552065) in view of Verner et al. (US 7276612) and Griffin et al. (US 2005/0020570) have been fully considered but they are not found persuasive

11. The rejection of claims 1, 2 and 4-14 made by the examiner under 35 USC 103(a) is **MAINTAINED** for the reasons of record in the office action mailed on 01/05/2009.

12. In regards to the 103(a) rejection, Applicant asserts the following:

B) None of the references teach HDAI compounds as having utility for the treatment of disease characterized by mutated FLT-3; and

C) the skilled artesian would not have had a reasonable basis to expect that the experiments would demonstrate that the combination of a FLT-3 inhibitor and HDAI to induce apoptosis of MV4-22 cells synergistically and induce apoptosis of the primary AML cells expressing FLT-3.

13. In response to B, the Examiner concedes Applicants point that none of the references disclose that AML is characterized by active mutant FLT-3. However, this does mitigate the current rejection because as a whole there is sufficient evidence demonstrating that HDAIs would be expected to have an inhibitory effect on cells expressing constitutively active mutant FLT-3. Verner teaches that HDAIs are useful for treating acute myeloid leukemia (AML). Griffin teaches teach that AML is characterized by mutations in FLT-3 receptors (see [0253]). Basic logic suggests the following:

HDAIs → treat AML;

AML → disease characterized by mutant FLT-3; therefore,

HDAIs → treat disease characterized by mutant FLT-3.

While Applicant is correct in that none of thee references explicitly states that HDAIs treat disease characterized by active mutant FLT-3, any ordinary person would still be perfectly capable of arriving at such a conclusion. Additionally, it's noted that the amendment to claim 1 may be interpreted so as only the solid tumor is characterized by cells that express constitutively active mutants FLT-3.

14. In response to C, the Examiner disagrees, and believes that an ordinary person would have a reasonable expectation that combining a FLT-3 inhibitor and an HDAI would be a useful

means for treating a condition characterized by active mutant FLT-3. As discussed above already, an ordinary skilled artesian would arrive at the conclusion that HDAIs are useful agents for treating AML, a disease characterized by active mutant FLT-3. Additionally, Griffin teaches that Midostaurin (Applicants claimed staurosprine derivative) is useful for treating AML. Thus any person would have been motivated to combine an HDAI and Midostaurin with a reasonable expectation for success that the combination would treat a disease like AML. Moreover, MPEP 2144.06(I) states that 'it is *prima facie* obvious to combine two compositions each of which is taught by the prior art as useful for the same purpose, in order to form a third composition to be used for the very same purpose'. In the present case, combining two methods, both of which are taught to be useful for a similar purpose, i.e. treating AML, in order to form a third new method used for the very same purpose, would flow logically from the art and be *prima facie* obvious. Applicant's arguments are not found persuasive.

Maintained Rejections, of Record
Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. **Claims 1, 2 and 4-14 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

17. The specification discloses chemicals which meet the written description and enablement

provisions of 35 USC 112, first paragraph. However, claims 1, 2 and 4-14 are directed to encompass undisclosed prodrugs and derivative compounds which only correspond in some undefined way to specifically instantly disclosed chemicals. In particular claim 1 recites the term "prodrug thereof," in regard to the HDAI component. None of the undisclosed compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

18. With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008,

> 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Applicant has failed to provide any detail with regard to an HDAI prodrug and what specifically an HDAI prodrug encompasses. Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. **Claims 1, 2 and 4-14 are rejected under 103(a) as being unpatentable over Remiszewski et al. (US 6,552,065; of record) in view of Verner et al. (US 7,276,612; of record) and Griffin et al. (US 2005/0020570; of record).**

23. Remiszewski teaches hydroxamate HDA inhibitor compounds, including applicant's elected compound, possess anti-prolfierative properties and have been studied for their therapeutic effects on cancer cells, (abstract; col. 1, lines 14-40; cols. 24-25, Example P3; see also cols. 115-116, **Compound 200 = applicant's elected HDAI**). Remiszewski teach that there remains a need for an active compound that is suitable for treating tumors, including cancerous tumors, that is highly efficacious and stable (col. 1, lines 14-40). Remiszewksi teach that even though butyric acid and its derivatives, including sodium phenylbutyrate, have been reported to induce apoptosis in vitro in human colon carcinoma, **leukemia** and retinoblastoma cell lines, these agents are not useful pharmacological agents because they tend to be metabolized rapidly and have a very short half-life in vivo (col. 1, lines 14-40).

24. Although Remiszewski exemplify applicant's elected HDAI compound species for use in treating leukemia, it does specifically teach AML (= applicant's elected disease species). Further, Remiszewski does not teach the instantly claimed combination of an HDAI (i.e. Compound 200) and an FLT-3 inhibitor (i.e. Midostaurin = applicant's elected FLT-3 inhibitor compound species).

25. Verner teaches that HDAIs are useful for treating various conditions, including AML, and may be co-administered with other therapeutic agents to treat said conditions (col. 49, line 20-35; col. 50, line 62 to col. 51, line 15; and col. 58, line 51 to col. 59, line 10). Verner does not specifically teach the instant claimed combination of a HDAI (e.g. Compound 200) and a FLT-3 inhibitor (e.g. Midostaurin) for treating AML.

26. Griffin teaches that aberrant expression of the FLT3 gene has been documented in both adult and childhood leukemias, including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AMLUTMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS)(see [0252]). Griffin teach that Midostaurin (or PKC42) possesses FLT-3 inhibitory properties that render it particularly useful as an inhibitor of FLT-3 receptors and especially in the treatment of leukemias and myelodysplastic syndromes (see [0232]-[0235]).

27. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Remiszewski, Verner and Griffin with a reasonable expectation for success in arriving at a method of treating AML by administering a FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin and a HDAI (e.g. Compound 200) as taught by Remiszewski for treating AML. One would have been motivated to do so because Vernier suggests that HDAIs may be combined with other agents to treat AML and therefore one

would have combined an HDAI (e.g. Compound 200) as taught by Remiszewski with another agent such as a FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin to treat AML since both classes of drugs are used to treat AML, as evidenced by the teaching of Vernier and Griffin. ((Cf. In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). Besides, Griffin teach that AML is associated with deregulated FLT-3 and therefore one would expect that the combination of an HDAI (e.g. Compound 200) as taught by Remiszewski with an FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin would also be effective in treating AML.

28. It is noted that Compound 200 as taught by Remiszewski is identical to applicant's elected HDAI compound species and reads on claims 1, 7, 8, 9, 10, 11, 12, 13 and 14.

29. It is noted that Midostaurin as taught by Griffin et al. is identical to applicant's elected FLT-3 inhibitor compound species and reads on claims 1, 4, 5, and 6.

30. It is noted that Griffiin and Verner teach AML (= applicant's elected disease species), which reads on claims 1 and 2.

31. Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

New Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

34. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35. **Claim 24 is rejected under 103(a) as being unpatentable over Remiszewski et al. (US 6,552,065; of record) in view of Verner et al. (US 7,276,612; of record) and Griffin et al. (US 2005/0020570; of record).**

36. Remiszewski, Verner and Griffin are discussed in detail above.

37. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Remiszewski, Verner and Griffin with a reasonable expectation for success in arriving at a method of treating AML by administering a FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin and a HDAI (e.g. Compound 200) as taught by Remiszewski for treating AML. One would have been motivated to do so because

Vernier suggests that HDAIs may be combined with other agents to treat AML and therefore one would have combined an HDAI (e.g. Compound 200) as taught by Remiszewski with another agent such as a FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin to treat AML since both classes of drugs are used to treat AML, as evidenced by the teaching of Vernier and Griffin. ((Cf. In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). Besides, Griffin teach that AML is associated with deregulated, mutant active FLT-3 and therefore one would expect that the combination of an HDAI (e.g. Compound 200) as taught by Remiszewski with an FLT-3 inhibitor (e.g. Midostaurin) as taught by Griffin would also be effective in treating AML. Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Conclusion

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

39. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

40. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

41.

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611